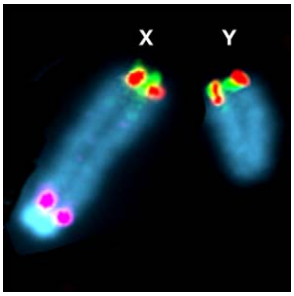
Ezrin Falls out of the Raft

Lipid rafts play an important role in B cell receptor signaling. Following engagement of the B cell receptor by antigen, lipid rafts coalesce to produce larger and more stable rafts. This event may concentrate important signaling molecules such as the B cell receptor and Src and Syk tyrosine kinases. However, according to Gupta et al. (2006), for the rafts to "up anchor," certain proteins must first detach themselves from their lipid neighbors. Gupta et al. compared the protein components of lipid rafts in the plasma membrane of antigen-stimulated and unstimulated B cells using quantitative mass spectrometry. They discovered that ezrin, a protein that links the plasma membrane to the actin cytoskeleton, was less abundant in lipid rafts following engagement of the B cell receptor by antigen. In addition, Ezrin is rapidly dephosphorylated at Threonine 567 following B cell receptor stimulation, which may contribute to its disassociation from both the lipid rafts and from the actin cytoskeleton. Untethering of the rafts from the cytoskeleton due to the loss of ezrin may enable the rafts to move and coalesce. In support of this hypothesis, a constitutively active ezrin that does not dissociate from the rafts blocked the coalescence of lipid rafts.

Although the localization of most proteins identified in their proteomic screen was unaffected by engagement of the B cell receptor with antigen, some proteins showed the opposite trend to ezrin and instead became enriched in lipid rafts. These include the B cell receptor itself, the nonmuscle myosin type 2A, and the myosin regulatory light chain. The next step will be to elucidate the mechanisms that underlie the recruitment of myosin proteins to lipid rafts and to determine whether myosin is critical for the cytoskeletal remodeling that promotes raft coalescence or for other functions that augment B cell receptor signaling.

N. Gupta et al. (2006). Nature Immunology. Published online April 30, 2006. 10.1038/ni1337.



FISH analysis of mouse embryonic fibroblasts reveals that the *Tlr7* gene (green) is found on both X and Y chromosomes of *Yaa* mutant mice but only on the X in wild-type animals. Image courtesy of S. Bolland.

Secrets of the Yaa Yaa Brotherhood

A genetic modifier on the Y chromosome, termed the Y-linked autoimmune accelerator (*Yaa*), increases the severity of autoimmune disease in a mouse model of Systemic Lupus Erythematosus. Recent work by Pisitkun et al. (2006) now identifies the *Yaa* locus as a region on the Y chromosome that is duplicated from the X chromosome. Interestingly, the duplicated region contains the gene for the Toll-like receptor 7 (TLR7), which recognizes single-strand RNA (ssRNA) during the innate immune response. This is a compelling finding because previous work has linked TLRs to B cell activation. The authors were able to show that the extra copy of TLR7 contributes to the accelerated onset and severity of lupus in mice. In B cells of *Yaa* mice, TLR7 expression is increased, and stimulation of spleen B cells with a TLR7 agonist is greater in *Yaa* mice than in wild-type mice. These results are consistent with the idea that autoreactive B cells can be activated by the synergistic engagement of B cell receptors and TLRs. Interestingly, previous work with this mouse model showed that the B cells in non-*Yaa* mice produce antibodies that recognize chromatin. In contrast, the autoreactive B cells of *Yaa* mice bind specifically to the nucleolus, a chromatin structure that contains ribosomal RNA. Pisitkun et al. suggest that the type of antigens that a TLR recognizes directly contributes to the activation of specific autoreactive B cells, in this case those that recognize ssRNA. It remains an open and intriguing question whether copy number variation in genes involved in TLR signaling contribute to the occurrence or severity of lupus, rheumatoid arthritis, or other autoimmune diseases in humans.

A related phenomenon may also occur as a result of TLR9 activation in B cells. TLR9 interacts with double-stranded DNA (dsDNA). Engagement of TLR9 of autoreactive B cells with dsDNA may contribute to the production of anti-chromatin autoantibodies. Fields et al. (2006) analyze this phenomenon in cultured B cells harvested from transgenic mice expressing a specific heavy chain variant that is frequently a component of autoantibodies in a mouse model of systemic lupus. Unlike B cells from wild type animals, a subset of B cells from the transgenic mice were found to proliferate spontaneously in culture, indicating the presence of endogenous activators. Such endogenous activators may stimulate TLR9 signaling because a ligand that inhibits TLR9 signaling blocked spontaneous B cell proliferation. Notably, most of these spontaneously proliferating B cells produced polyreactive antibodies (that is, antibodies that display nonspecific binding to many different antigens including chromatin). However, one B cell clone showed specific reactivity to chromatin. This may have relevance for autoimmune diseases as patients with lupus have more polyreactive antibodies than healthy individuals. The Fields et al. study suggests that this may be a consequence of enhanced TLR signaling.

P. Pisitkun et al. (2006). Science. Published online May 18, 2006. 10.1126/science.1124978.
M.L. Fields et al. (2006). J. Immunol. ***176****, 6491–6502.*

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